

General

Guideline Title

Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors. Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology.

Bibliographic Source(s)

Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, Thunnissen E, Ladanyi M. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors. Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer [trunc]. Arch Pathol Lab Med. 2013 Jun;137(6):828-860. [322 references] [PubMed](#)

Guideline Status

This is the current release of this guideline.

Recommendations

Major Recommendations

The grades of recommendation (A-D) and the strength of evidence (I-IV) are defined at the end of the "Major Recommendations" field.

SECTION I: When Should Molecular Testing of Lung Cancers Be Performed?

Question 1: Which Patients Should Be Tested for *Epidermal Growth Factor Receptor (EGFR)* Mutations and *Anaplastic Lymphoma Kinase (ALK)* Rearrangements?

1.1a: Recommendation. *EGFR* molecular testing should be used to select patients for EGFR-targeted tyrosine kinase inhibitor (TKI) therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

1.1b: Recommendation. *ALK* molecular testing should be used to select patients for ALK-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics. Evidence Grade: EGFR A; ALK: B

1.2: Recommendation. In the setting of lung cancer resection specimens, *EGFR* and *ALK* testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade. In the setting of fully excised lung cancer specimens, *EGFR* and *ALK* testing is not recommended in lung cancers that lack any adenocarcinoma component, such as "pure" squamous cell carcinomas, "pure" small cell carcinomas, or large cell carcinomas lacking any immunohistochemistry (IHC) evidence of adenocarcinoma differentiation. Evidence Grade: EGFR and ALK: A

1.3: Recommendation. In the setting of more limited lung cancer specimens (biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, *EGFR* and *ALK* testing may be performed in cases showing squamous or small cell histology but clinical criteria (e.g., young

age, lack of smoking history) may be useful in selecting a subset of these samples for testing. Evidence Grade: EGFR and ALK: A

1.4: Recommendation. To determine *EGFR* and *ALK* status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing. Evidence Grade: EGFR and ALK: B

1.5: Expert consensus opinion. For patients with multiple, apparently separate, primary lung adenocarcinomas, each tumor may be tested but testing of multiple different areas within a single tumor is not necessary.

Question 2: When Should a Patient Specimen Be Tested for *EGFR* Mutation or *ALK* Rearrangement?

2.1a: Recommendation. *EGFR* mutation testing should be ordered at the time of diagnosis for patients presenting with advanced-stage disease (stage IV according to the 7th edition tumor, node, metastasis [TNM] staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower-stage disease but were not previously tested.

2.1b: Suggestion. *ALK* rearrangement testing should be ordered at the time of diagnosis for patients presenting with advanced-stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower-stage disease but were not previously tested. Evidence Grade: EGFR: A; ALK: C

2.2a: Expert consensus opinion. *EGFR* testing of tumors at diagnosis from patients presenting with stage I, II, or III disease is encouraged but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

2.2b: Expert consensus opinion. *ALK* testing of tumors at diagnosis from patients presenting with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

2.3 Recommendation. Tissue should be prioritized for *EGFR* and *ALK* testing. Evidence Grade: EGFR: A; ALK: B

Question 3: How Rapidly Should Test Results Be Available?

3.1: Expert consensus opinion. *EGFR* and *ALK* results should be available within 2 weeks (10 working days) of receiving the specimen in the testing laboratory.

3.2: Expert consensus opinion. Laboratories with average turnaround times beyond 2 weeks need to make available a more rapid test—either in-house or through a reference laboratory—in instances of clinical urgency.

3.3: Expert consensus opinion. Laboratory departments should establish processes to ensure that specimens that have a final histopathologic diagnosis are sent to outside molecular pathology laboratories within 3 working days of receiving requests and to intramural molecular pathology laboratories within 24 hours.

SECTION II: How Should *EGFR* Testing Be Performed?

Question 4: How Should Specimens Be Processed for *EGFR* Mutation Testing?

4.1: Expert consensus opinion. Pathologists should use formalin-fixed, paraffin-embedded (FFPE) specimens or fresh, frozen, or alcohol-fixed specimens for polymerase chain reaction (PCR)-based *EGFR* mutation tests. Other tissue treatments (e.g., acidic or heavy metal fixatives, or decalcifying solutions) should be avoided in specimens destined for *EGFR* testing.

4.2: Expert consensus opinion. Cytologic samples are also suitable for *EGFR* and *ALK* testing, with cell blocks being preferred over smear preparations.

Question 5: What Are the Specimen Requirements for *EGFR* Testing?

5.1: Expert consensus opinion. Pathologists should determine the adequacy of specimens for *EGFR* testing by assessing cancer cell content and deoxyribonucleic acid (DNA) quantity and quality.

5.2: Expert consensus opinion. Each laboratory should establish the minimum proportion and number of cancer cells needed for mutation detection during validation.

5.3: Expert consensus opinion. A pathologist should assess the tumor content of each specimen and either perform, or guide a trained technologist to perform, microdissection for tumor cell enrichment as needed.

Question 6: How Should *EGFR* Testing Be Performed?

6.1: *Recommendation*. Laboratories may use any validated *EGFR* testing method with sufficient performance characteristics. Evidence Grade: B

6.2: *Expert consensus opinion*. Laboratories should use *EGFR* test methods that are able to detect mutations in specimens with at least 50% cancer cell content, although laboratories are strongly encouraged to use (or have available at an external reference laboratory) more sensitive tests that are able to detect mutations in specimens with as little as 10% cancer cells.

6.3: *Expert consensus opinion*. Clinical *EGFR* mutation testing should be able to detect all individual mutations that have been reported with a frequency of at least 1% of *EGFR*-mutated lung adenocarcinomas.

6.4: *Recommendation*. Immunohistochemistry for total *EGFR* is not recommended for selection of *EGFR* TKI therapy. Evidence Grade: A

6.5: *Recommendation*. *EGFR* copy number analysis (i.e., fluorescence in situ hybridization [FISH] or chromogenic in situ hybridization [CISH]) is not recommended for selection of *EGFR* TKI therapy. Evidence Grade: B

Question 7: What Is the Role of *KRAS* Analysis in Selecting Patients for Targeted Therapy With *EGFR* TKIs?

7.1: *Recommendation*. *KRAS* mutation testing is not recommended as a sole determinant of *EGFR* TKI therapy. Evidence Grade: B

Question 8: What Additional Testing Considerations Are Important in the Setting of Secondary or Acquired *EGFR* TKI Resistance?

8.1: *Recommendation*. If a laboratory performs testing on specimens from patients with acquired resistance to *EGFR* kinase inhibitors, such tests should be able to detect the secondary *EGFR* T790M mutation in as few as 5% of cells. Evidence Grade: B

SECTION III: How Should *ALK* Testing Be Performed?

Question 9: What Methods Should Be Used for *ALK* Testing?

9.1: *Recommendation*. Laboratories should use an *ALK* FISH assay using dual-labeled break-apart probes for selecting patients for *ALK* TKI therapy; *ALK* immunohistochemistry, if carefully validated, may be considered as a screening methodology to select specimens for *ALK* FISH testing. Evidence Grade: B

9.2: *Recommendation*. Reverse transcription-polymerase chain reaction (RT-PCR) is not recommended as an alternative to FISH for selecting patients for *ALK* inhibitor therapy. Evidence Grade: B

9.3: *Expert consensus opinion*. A pathologist should be involved in the selection of sections for *ALK* FISH testing, by assessing tumor architecture, cytology, and specimen quality.

9.4: *Expert consensus opinion*. A pathologist should participate in the interpretation of *ALK* FISH slides, either by performing the analysis directly or by reviewing the interpretations of cytogeneticists or technologists with specialized training in solid tumor FISH analysis.

9.5: *Expert consensus opinion*. Testing for secondary mutations in *ALK* associated with acquired resistance to *ALK* inhibitors is not currently required for clinical management.

SECTION IV: Should Other Genes Be Routinely Tested in Lung Adenocarcinoma?

Question 10: Are Other Molecular Markers Suitable for Testing in Lung Cancer?

10.1a: *Recommendation*. Testing for *EGFR* should be prioritized over other molecular markers in lung adenocarcinoma.

10.1b: *Suggestion*. After *EGFR* testing, testing for *ALK* should be prioritized over other proposed molecular markers in lung adenocarcinoma, for which published evidence is insufficient to support testing guideline development at the present time. Evidence Grade: *EGFR*: A; *ALK*: C

SECTION V: How Should Molecular Testing of Lung Adenocarcinomas Be Implemented and Operationalized?

Question 11: Must All Adenocarcinomas Be Tested for Both *EGFR* and *ALK*?

11.1: *Expert consensus opinion*. Laboratories may implement testing algorithms to enhance the efficiency of molecular testing of lung adenocarcinomas, provided the overall turnaround time requirements are met.

Question 12: How Should *EGFR* and *ALK* Results Be Reported?

12.1: *Expert consensus opinion*. *EGFR* mutation testing reports and *ALK* FISH reports should include a results and interpretation section readily understandable by oncologists and by nonspecialist pathologists.

Question 13: How Should *EGFR* and *ALK* Testing Be Validated?

13.1: Expert consensus opinion. *EGFR* and *ALK* testing validation should follow the same guidelines as for other molecular diagnostics and FISH tests.

Question 14: How Should Quality Assurance Be Maintained?

14.1: Expert consensus opinion. Laboratories should follow similar quality control and quality assurance policies and procedures for *EGFR* and *ALK* testing in lung cancers as for other clinical laboratory assays. In particular, laboratories performing *EGFR* and *ALK* testing for TKI therapy should enroll in proficiency testing, if available.

Definitions:

Definition of Grades of Recommendations

Grade of Recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Hierarchy of Evidence

Level	Intervention
I	A systematic review of level II studies
II	Randomized controlled trial (RCT) (good quality)
III-1	A pseudo-RCT (i.e., alternate allocation or some other method) or RCT (poor quality)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none">• Non-randomized, experimental trial• Cohort study, case-control study, Interrupted time series with a control group (good quality)
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none">• Historical control study• Cohort study, case-control study, interrupted time series with a control group (poor quality)• Interrupted time series without a parallel control group• Two or more single arm studies
IV	Case series with either post-test or pre-test/post-test outcomes

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Lung cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Diagnosis

Evaluation

Treatment

Clinical Specialty

Internal Medicine

Medical Genetics

Oncology

Pathology

Pulmonary Medicine

Intended Users

Physicians

Guideline Objective(s)

To establish evidence-based recommendations for the molecular analysis of lung cancers that are required to guide epidermal growth factor receptor (*EGFR*)- and anaplastic lymphoma kinase (*ALK*)-directed therapies, addressing which patients and samples should be tested, and when and how testing should be performed

Target Population

Patients with a diagnosis of non–small cell lung cancer (NSCLC)

Interventions and Practices Considered

1. *Epidermal growth factor receptor (EGFR)* molecular testing, including timing of test, selection of test method, and type of specimen
2. *Anaplastic lymphoma kinase (ALK)* molecular testing, including timing of test and type of specimen
3. Involvement of a pathologist in selection of *ALK* fluorescence in situ hybridization (FISH) specimen and interpretation of slides
4. Reporting and validation of test results

Note: The following were considered but not recommended: immunohistochemistry for total EGFR for selection of EGFR tyrosine kinase inhibitor (TKI) therapy; EGFR copy number analysis (i.e., FISH or chromogenic in situ hybridization [CISH]) for selection of EGFR TKI therapy; KRAS mutation testing as a sole determinant of EGFR TKI therapy; reverse transcriptase-polymerase chain reaction (RT-PCR) as an alternative to FISH for selecting patients for ALK inhibitor therapy.

Major Outcomes Considered

- Response rate
- Disease control rate
- Overall survival at 1 year
- Time to disease progression
- Progression-free survival
- Median survival time

- Sensitivity, specificity, positive predictive value, and negative predictive value of tests to determine epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) status or treatment response
- Correlations between EGFR mutation or ALK rearrangement and benefit from EGFR or ALK tyrosine kinase inhibitor (TKI) therapies, respectively
- Accuracy in determining EGFR or ALK status
- Concordance across technical platforms

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Systematic Literature Review and Analysis

The literature search strategy involved searching the following electronic databases from January 2004 through February 2012: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-indexed Citations, and the Wiley Cochrane Library. The following keywords and MeSH terms were used in the search: *lung neoplasms, lung cancer, carcinoma, non-small-cell lung, EGFR, Epidermal growth factor receptor, ALK, KRAS, BRAF, mutation, amplification, gene copy number, rearrangement, fusion, translocation, inversion, immunohistochemistry, IHC, and FISH*. All searches were limited to the English language.

Eligible Study Designs

Systematic reviews with or without meta-analyses, randomized controlled trials, cohort studies, case-control studies, case series, and method comparisons were eligible for this study. Also included were testing guidelines and proficiency testing strategies of various U.S. and international organizations.

Inclusion Criteria

Articles were eligible for inclusion if they met the following criteria:

1. The study compared, prospectively or retrospectively, the sensitivity, specificity, negative predictive value, or positive predictive value of *epidermal growth factor receptor (EGFR)* or *anaplastic lymphoma kinase (ALK)* tests for detection of an *EGFR* mutation, *ALK* rearrangement, or response to a targeted *EGFR* or *ALK* tyrosine kinase inhibitor (TKI); the study described technical comparisons across various assay platforms; the study examined potential testing algorithms for non-small cell lung cancer (NSCLC) molecular testing; or the study examined the correlation of *EGFR* or *ALK* status in primary versus metastatic tumors from the same patients.
2. The study population consisted of patients with a diagnosis of NSCLC.
3. The primary outcomes included the sensitivity, specificity, positive predictive value, and negative predictive value of tests to determine *EGFR* or *ALK* status or treatment response, alone and in combination; concordance across platforms; and accuracy in determining *EGFR* or *ALK* status and benefit from anti-*EGFR* or *ALK* TKI therapy.

Exclusion Criteria

Letters, commentaries, editorials, reviews, and case reports were excluded.

Tests Examined

Additional test methods considered included *EGFR* copy number by fluorescence in situ hybridization (FISH) or bright-field chromogenic in situ hybridization (CISH), immunohistochemistry for expression of *ALK* (kinase domain or carboxy-terminal) or mutated *EGFR* protein, and reverse transcription-polymerase chain reaction (RT-PCR) detection of *EML4-ALK* fusion transcript. Alterations in other genes, including *KRAS*, *BRAF*, and *MET*, were also considered.

Outcomes of Interest

The primary outcomes of interest were the correlations between *EGFR* mutation or *ALK* rearrangement and benefit from EGFR or ALK TKI therapies, respectively. Other outcomes of interest included accuracy in determining *EGFR* or *ALK* status, concordance across technical platforms, sensitivity, and specificity of different tests. After careful consideration of each of these, the expert panel and advisory panel agreed that the primary recommendations of this guideline should focus on *EGFR* mutation assays and *ALK* FISH assays.

The panel reviewed the results of randomized controlled trials in lung cancer testing anti-EGFR or ALK therapies such as gefitinib, erlotinib and crizotinib. The panel also reviewed unblinded trials comparing various testing methods, describing test characteristics, and defining strategies for quality assurance of testing in the literature.

Environmental Scan

Individuals representing regulatory agencies (U.S. Food and Drug Administration) also provided information about the regulatory framework. Individuals involved with quality assurance in the United States (College of American Pathologists [CAP]), the Netherlands, and Canada (Province of Ontario) also provided information about programs to measure and improve *EGFR* and *ALK* testing. This information was used to help the panel specify testing requirements and exclusions, and the necessary quality assurance monitoring that will make the testing less variable and more accurate.

Number of Source Documents

521 pertinent articles were reviewed in detail for their relevance to the recommendations.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Hierarchy of Evidence

Level	Intervention
I	A systematic review of level II studies
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IV	Case series with either post-test or pre-test/post-test outcomes

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Description of the Methods Used to Analyze the Evidence

Grading of the Included Evidence

For strength of the evidence, the expert panel considered the level of evidence based on its hierarchy, number of studies and number of patients, magnitude of effect from the weighted mean difference or risk ratio, statistical precision measured as a point estimate or confidence interval, and methodologic quality of included studies. The quality of systematic reviews, randomized control trials, and cohort studies was assessed by using the AMSTAR (Assessment of Multiple Systematic Reviews) instrument and SIGN (Scottish Intercollegiate Guidelines Network) 50 checklists, respectively.

Both clinical (variation in patients, intervention, comparator, outcome) and statistical heterogeneity (measured as P value and I^2) were assessed. The scores from evidence base and consistency were obtained based on individual components. An emphasis was given to patient-oriented outcomes rather than disease-oriented outcomes. These scores were presented to panel members, who then provided scores for clinical impact, generalizability, and applicability of the evidence (as explained briefly in Table 2 of the Supplemental Digital Content; see the "Availability of Companion Documents" field) all scores were then collated.

College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP) Expert Panel Literature Review and Analysis

The expert panel coauthors (N.I.L., P.T.C., M.L.) reviewed 1,533 potentially relevant abstracts identified in the original literature searches to select studies pertinent to the guideline: 2 coauthors independently reviewed each abstract, and disagreements were resolved by the third coauthor. Full-text articles (521) were then reviewed for all selected abstracts by 2 members of the expert author panel; discrepancies were resolved by a coauthor. Evidence tables were developed from selected studies that met the criteria for inclusion. A third literature review was performed by the authors of each section of the guideline, to verify that the highest levels of evidence supported each of their recommendations and, if not, to re-evaluate the recommendation and modify or defend it.

A total of 278 studies were selected. In studies with duplicate data (companion publications), the original study, or the study reporting detailed or recent data (with a higher number of patients) was included. In cases where different outcomes had been reported, all studies were included.

A methodologist performed the original data extraction, and this was verified by CAP technical staff. All analyses were performed using the Review Manager (RevMan) computer program (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Analyses were performed for main comparisons as well as subgroup-analyses where warranted. Intention-to-treat data were analyzed where possible; otherwise, per-protocol data were used. Mean differences (MD) with 95% confidence intervals (CI) were calculated for continuous data and relative risk ratio (RR) with 95% CI were calculated for dichotomous data; values of $P < .05$ were considered to be statistically significant. Where mean data were not available, median data were used based on the assumption of constant hazard, but were calculated and presented separately. The random effects model was used for all analyses, as it is the more conservative estimate of treatment effect. Comparative data were pooled where no clinical heterogeneity was present, as determined by the expert panel coauthors. The magnitude of statistical heterogeneity was calculated using the I^2 statistic for all pooled comparisons using the methods described by Montori et al (2008) where a value of 0%–25% indicated low, 26%–50% indicated moderate, and greater than 51% indicated large heterogeneity. For I^2 values greater than 75%, sub-group analysis to explore possible sources of heterogeneity would be considered. See Table 4 (of the Supplemental Digital Content; see the "Availability of Companion Documents" field) for a summary of the I^2 values obtained.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Panel Composition

The College of American Pathologists (CAP) Pathology and Laboratory Quality Center, and representatives from the International Association for the Study of Lung Cancer (IASLC) and Association for Molecular Pathology (AMP), jointly convened an expert author panel and scientific

advisory panel consisting of experts in clinical pathology and oncology, and research and development relevant to molecular testing in non-small cell lung cancer (NSCLC). A conference with the expert author and advisory panels was held in December 2010, at which representatives from industry, public health policy and regulatory affairs, patient advocacy, and commercial drug and/or diagnostic device manufacturers were invited to participate. Representatives from the U.S. Food and Drug Administration (FDA), the National Cancer Institute, American Society for Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) attended the conference. The opinions of panel members associated with official government agencies represent their individual views and not necessarily those of the agency with which they are affiliated.

Consensus Development Based on Evidence

The entire panel met in December 2010 (Chicago, Illinois); additional work on the guideline was completed through electronic mail and monthly teleconferences of the coauthors and/or expert panel. The purposes of the panel meeting were to refine the questions addressed by the guideline, solicit input and testimony from the nonwriting advisory panel, and make writing assignments for the respective sections. All members of the expert panel participated in the preparation of the draft guideline, which was then disseminated for review by the entire panel.

Quality Assessment and Grading of the Included Evidence

Grading of recommendations was based on overall ratings of individual components of the evidence, such as strength of evidence, its consistency, clinical impact, generalizability, and applicability to the international health care system.

Rating Scheme for the Strength of the Recommendations

Definition of Grades of Recommendations

Grade of Recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Feedback on the draft recommendations was solicited from external reviewers. The open comment period was held from November 21, 2011 to December 20, 2011. An announcement was sent to the following organizations:

- CAP Board of Governors, Councils, Committees and Membership
- International Association for the Study of Lung Cancer (IASLC)
- Association for Molecular Pathology (AMP)
- American Society for Clinical Oncology (ASCO)
- American Society for Clinical Pathology (ASCP)
- US Food and Drug Administration (FDA)
- United States & Canadian Academy of Pathology (USCAP)
- American Cancer Society

- American Lung Association
- National Lung Cancer Partnership
- Lung Cancer Foundation of America
- Uniting Against Lung Cancer
- Addario Lung Cancer Medical Institute (ALCMI)
- European Society for Medical Oncology (ESMO)
- American Association for Clinical Chemistry (AACC)

The website received 528 comments in total. The expert panel cochairs reviewed all comments and responses (i.e., agreed, disagreed or unsure). The cochairs documented their action for each recommendation as maintain original recommendation; revise with minor language change, or consider major recommendation change. The expert panel cochairs then met with the expert panel via WebEx to discuss their decisions to address these comments and finalize the recommendations. The guideline and method supplement were reviewed by a CAP independent review panel and approved by the CAP Transformation Program Office Steering Committee, by the IASLC Board of Directors, and by the AMP Clinical Practice Committee and Executive Council.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- If an epidermal growth factor receptor (*EGFR*) mutation is discovered in any tumor, the patient may benefit from an EGFR tyrosine kinase inhibitor (TKI).
- Testing the initial surgical specimen at the time of resection affords the benefits of having recent tissue to test as well as, in many instances, larger resection specimens with ample material.
- The main benefit of dissection is the production of relatively pure specimens of a morphologically confirmed cell population.
- Recent data suggest that acquired resistance (AR) patients with the T790M mutation can derive continued clinical benefit from the first-line EGFR TKI.

Potential Harms

- False negative or false positive results
- In specimens with high tumor content, if an ultrasensitive molecular assay finding is positive while an assay finding of conventional sensitivity is negative, the result is either interpreted as a possible false positive due to mispriming or low cross-contamination, or as a true positive reflecting a very small mutated subclone. Thus, there is a risk of losing specificity with regard to predicting response to targeted therapy. Some studies using such methods have found novel, possibly artifactual mutations, or failed to show a relationship between classic *epidermal growth factor receptor (EGFR)* mutations and treatment response. Finally, technical artifacts may be seen with ultrasensitive methods that require experience and caution in interpretation.

Qualifying Statements

Qualifying Statements

- Clinical practice guidelines and consensus statements reflect the best available evidence and expert consensus supported in practice. They are intended to assist physicians and patients in clinical decision making and to identify questions and settings for further research. With the

rapid flow of scientific information, new evidence may emerge between the time a practice guideline or consensus statement is developed and when it is published or read. Guidelines and statements are not continually updated and may not reflect the most recent evidence. Guidelines and statements address only the topics specifically identified therein and are not applicable to other interventions, diseases, or stages of diseases. Furthermore, guidelines and statements cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician, relying on independent experience and knowledge, to determine the best course of treatment for the patient. Accordingly, adherence to any practice guideline or consensus statement is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances and preferences. The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) make no warranty, express or implied, regarding guidelines and statements and specifically exclude any warranties of merchantability and fitness for a particular use or purpose. CAP, IASLC, and AMP assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this statement or for any errors or omissions.

- In formulating recommendations for molecular testing in lung cancer, CAP, IASLC, and AMP considered these tenets of guideline development, emphasizing review of data from appropriately conducted and analyzed clinical trials. Practice guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The literature and expert review process was directed toward evaluating and selecting the best science for the best possible patient care; a cost analysis was not performed for this guideline.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, Thunnissen E, Ladanyi M. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors. Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer [trunc]. Arch Pathol Lab Med. 2013 Jun;137(6):828-860. [322 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Jun

Guideline Developer(s)

Association for Molecular Pathology - Medical Specialty Society

College of American Pathologists - Medical Specialty Society

International Association for the Study of Lung Cancer - Disease Specific Society

Source(s) of Funding

The College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology provided funding for this project; no industry funds were used in the development of the guideline.

Guideline Committee

College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Expert Panel

Composition of Group That Authored the Guideline

Expert Panel Members: Neal I. Lindeman, MD, Department of Pathology, Brigham & Women's Hospital, Boston, Massachusetts; Philip T. Cagle, MD, Department of Pathology and Genomic Medicine, The Methodist Hospital, Houston, Texas; Mary Beth Beasley, MD, Department of Pathology, Mt Sinai Medical Center, New York, New York; Dhananjay Arun Chitale, MD, Department of Pathology, Henry Ford Hospital, Detroit, Michigan; Sanja Dacic, MD, PhD, Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Giuseppe Giaccone, MD, PhD, Medical Oncology Branch, National Institutes of Health, Bethesda, Maryland; Robert Brian Jenkins, MD, PhD, Department of Laboratory Medicine and Pathology, Department of Laboratory Genetics, Mayo Clinic, Rochester, Minnesota; David J. Kwiatkowski, MD, PhD, Department of Medicine, Brigham & Women's Hospital, Boston, Massachusetts; Juan-Sebastian Saldivar, MD, Department of Pathology, City of Hope National Medical Center, Duarte, California; Jeremy Squire, PhD, Department of Pathology and Molecular Medicine, Kingston General Hospital, Queen's University, Kingston, Ontario, Canada; Erik Thunnissen, MD, PhD, Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands; Marc Ladanyi, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York

Financial Disclosures/Conflicts of Interest

Conflict of Interest Policy

Before acceptance on the expert panel, potential member authors from all guideline partnering organizations completed the College of American Pathologists (CAP) conflict of interest process, whose policy and form requires disclosure of material financial interest in, or potential for benefit of significant value from, the guideline's development or its recommendations beginning 12 months prior and ending when the guideline was submitted for publication (see the Appendix to the original guideline document). The potential members completed the conflict of interest disclosure form conservatively, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. Regarding members declaring potentially perceived or real conflict, guideline coauthors agreed that these individuals would best serve as advisory panel members for the guideline, but not authors on the expert panel.

See the supplemental digital content (see the "Availability of Companion Documents" field) for the conflict of interest policy.

Guideline Status

This is the current release of this guideline.

Guideline Availability

Electronic copies: Available from the [Archives of Pathology & Laboratory Medicine Web site](#) .

Availability of Companion Documents

The following are available:

- Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors. Summary of recommendations. 2013 Apr 3. 3 p. Electronic copies: Available in Portable Document Format (PDF) from the [College of American Pathologists \(CAP\) Web site](#) .
- Frequently asked questions (FAQs) in regard to molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors. 2013 Apr 3. 2 p. Electronic copies: Available in PDF from the [CAP Web site](#) .

Supplemental digital content is available from the [Archives of Pathology & Laboratory Medicine Web site](#) .

Patient Resources

The following is available:

- What to know: the CAP/IASLC/AMP guideline on test selection for *EGFR* mutation and *ALK* rearrangement in lung cancer. Patient guide. 2013 Apr. 2 p. Electronic copies: Available from the [College of American Pathologists Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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